REMARKS

Claims 1-35 are pending in the application. Claims 1-5 and 16-35 have been withdrawn. Claims 11-15 are currently under examination. Claim 11 is amended herein for clarity and to more particularly define the invention. Support for the amendments to claim 11 can be found in the claims as filed, in the specification on page 14, lines 1-13, in the Examples, in Figures 5-7, and elsewhere throughout the specification. No new matter is believed to be added by these amendments. Therefore, Applicants respectfully request entry of these amendments and allowance of the claims to issue.

Sequence Non-Compliance

According to the Office Action, there are sequences present on pages 19 and 22 of the specification that do not have a corresponding Sequence Listing, CRF or SEQ ID NOs. In response, the specification is amended herein to identify the sequences set forth on pages 19 and 22 with a SEQ ID number. A Sequence Listing that includes all of the sequences set forth on pages 19 and 22 is enclosed herewith. Also enclosed is a diskette containing the Sequence Listing for this application in computer readable form (CRF) and a paper copy of the Sequence Listing in compliance with 37 C.F.R. § 1.821-1.825. Applicants hereby certify that the information in the computer readable form on the diskette and in the hard copy of the Sequence Listing is the same and includes no new matter. The enclosed computer readable copy and paper copy of the Sequence Listing are believed to bring the Sequence Listing into full compliance with the sequence rules. Therefore, Applicants believe that the objections regarding the sequences set forth in the Application have been overcome. Thus, Applicants respectfully request their withdrawal.

Rejection Under 35 U.S.C. § 112, first paragraph

The Office Action states that claims 11-14 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for a method for identifying a blood vessel related gene that is involved in blood vessel growth comprising a) providing a first transgenic zebrafish expressing a fluorescent reporter protein in blood

vessels and a second transgenic zebrafish expressing a fluorescent reporter protein in blood vessels and additionally comprising an altered gene that results in altered gene product activity; and b) determining whether the altered gene has an effect on blood vessel growth by comparing blood vessel morphology of said first transgenic zebrafish to blood vessel morphology of said second transgenic zebrafish, wherein a difference in blood vessel morphology is indicative of a blood vessel related gene involved in blood vessel growth allegedly does not reasonably provide enablement for a method of identifying a blood vessel related gene that is involved in blood vessel growth comprising comparing 1) any measurable characteristic other than blood vessel growth in a transgenic zebrafish containing blood vessels that express 2) any reporter gene with a transgenic zebrafish containing blood vessels that express any reporter gene and has an 3) alteration in a blood vessel related gene that does not result in an altered gene product activity and determining the effect of the altered blood vessel related gene on blood vessel growth such that if there is any difference between the blood vessels of the transgenic zebrafish, the blood vessel related gene is involved in blood vessel growth.

In response to the Examiner's comments regarding measurable characteristics, claim 11 is amended herein to specify that "blood vessel growth" is the characteristic that is being measured.

On page 8 of the Office Action, the Examiner alleges that the claimed novelty of the instant invention is the use of a fluorescent reporter gene which allow for *in vivo* assays in the zebrafish. Further stated in the paragraph bridging pages 8 and 9 of the Office Action, is that for an artisan to utilize the novel improvement proposed by the instant invention, they would specifically need to use a fluorescent reporter gene to visualize differences in blood vessel growth and development and that an artisan would allegedly not know how to use a reporter gene that does not allow for *in vivo* detection in the claimed invention as disclosed by the specification.

Although Applicants have disclosed *in vivo* assays utilizing fluorescent report genes, it would be clear to one of skill in the art that other reporter genes can be utilized in the claimed methods. As set forth on page 9 of the specification, the reporter protein

can be detected by methods known in the art. For example, RNA can be detected utilizing nucleic acid detection techniques. Antibodies can also be used to detect the expression product. One of skill in the art would also know how to utilize other reporter proteins, such as β-galactosidase, luciferase or alkaline phosphatase, which produce a detectable product. Assays for detection of these products are routinely performed by the skilled artisan. Therefore, contrary to the Office Action's conclusion, one of skill in the art would know how to use and detect a non-fluorescent reporter protein in the methods claimed herein.

On page 9 of the Office Action, it is stated that not all alterations that can be made to a blood vessel related gene will result in an alteration in gene product activity. Further stated on page 9 is that because this assay relies upon the alteration that results in a phenotypic difference that is a result of an alteration in a gene product activity of the altered gene, an artisan would allegedly not be able to use the instant assay with an altered gene that did not have an alteration that resulted in an alteration in gene product activity, because the artisan would not be able to determine a phenotypic difference in blood vessel growth and therefore would allegedly not be able to determine if the altered gene is involved in blood vessel growth as is required by the claims.

As amended herein, claim 11 now specifies that the alteration results in an alteration of blood vessel related gene product activity. Applicants have shown that a blood vessel related gene can be altered in order to alter blood vessel related gene product activity. This alteration in blood vessel related gene product activity results in a phenotypic difference, for example, a difference in blood vessel growth, that can be readily identified.

Applicants believe that claims 11-14 are adequately enabled and respectfully request withdrawal of this rejection.

Rejection Under 35 U.S.C. § 112, second paragraph

The Office Action states that claims 11-15 are rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite for failing to particularly point out and

distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner has indicated that it is not clear whether from the claims if the method is meant to determine differences in blood vessel growth or gene alteration.

As set forth above, claim 11 is amended herein to specify that differences in blood vessel growth are being determined. Therefore, Applicants believe this rejection has been overcome and respectfully request its withdrawal as it applies to claims 11-15.

Rejection Under 35 U.S.C. § 102(b)

The Office Action states that claims 11 and 12 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Motoike et al. (*Genesis* 28: 75-81, 2000). According to the Office Action, Motoike et al. disclose a transgenic zebrafish comprising a GFP reporter gene operably linked to the Tie2 promoter (paragraph bridging p. 76-77). Tie2 is a blood vessel specific gene that is expressed during blood vessel growth and development. The Office Action further states that Motoike et al. also discloses that this zebrafish system will be useful for the study of vascular development and that these zebrafish can be crossed to various existing mutant lines of zebrafish, which have altered vascular development, to investigate morphological changes in vascular growth. According to the Examiner, because Motoike et al. discloses crossing the Tie2-GFP zebrafish with mutants that already exist, they are providing zebrafish with both the Tie2-GFP reporter gene and a known, altered blood vessel related gene as claimed. Furthermore, the Office Action assumes that because the Tie2-GFP is disclosed as being blood vessel specific to be used in assays of vascular growth and development, they also disclose the means of comparing the two zebrafish and identifying a blood vessel related gene involved in blood vessel growth.

Applicants respectfully point out that claim 11 requires a comparison between a transgenic zebrafish containing blood vessels that express a reporter protein with a transgenic zebrafish containing blood vessels that express a reporter protein and an altered blood vessel related gene. Although Motoike et al. discloses crossing the Tie2-GFP fish with mutant fish, nowhere in Motoike et al. is it disclosed that this fish was obtained, much less that a comparison of blood vessel growth between a Tie2-GFP

zebrafish and the zebrafish resulting from a Tie2-GFP zebrafish crossed with a mutant zebrafish was performed. Furthermore, nowhere in Motoike et al. is it disclosed that any difference in blood vessel growth between the two fish was observed in order to identify a blood vessel related gene involved in blood vessel growth. Applicants remind the Examiner that a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. It is clear that Motoike et al. does not expressly or inherently disclose every element of the claim. Thus, Applicants believe that Motoike et al. does not anticipate claims 11-15 and respectfully request withdrawal of this rejection.

Rejection Under 35 U.S.C. § 103(a)

The Office Action states that claims 13 and 14 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Motoike et al. as applied to claims 11 and 12 above, and further in view of Matz et al. (*Nature* 17: 969-973).

Although Motoike et al. discloses crossing the Tie2-GFP fish with mutant fish, nowhere in Motoike et al. is it disclosed that this fish could be obtained, such that a comparison of blood vessel growth between a Tie2-GFP zebrafish and the zebrafish resulting from a Tie2-GFP zebrafish crossed with a mutant zebrafish could be performed in order to identify a blood vessel related gene that is involved in blood vessel growth. Simply because Motoike et al. discloses that the Tie2-GFP zebrafish can be used to visualize vascular development, does not mean that any changes in blood vessels resulting from an altered blood vessel related gene could also be assessed in a zebrafish resulting from a cross between a Tie2-GFP zebrafish and a mutant zebrafish. In other words, just because blood vessels can be visualized for developmental purposes and a reporter protein can be expressed in blood vessels, this does not mean that any changes in blood vessel growth caused by a mutant or altered gene could also be observed in these zebrafish in order to identify a blood vessel related gene that is involved in blood vessel growth, at the time of the present invention. Until the present invention, there was no evidence that changes, if any, would be observed upon altering a blood vessel related gene in a zebrafish that expresses a reporter protein in blood vessels. Applicants were the

first to show that such changes could be observed and associated with a blood vessel related gene.

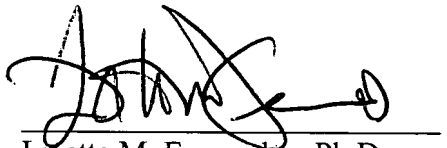
In this regard, Applicant respectfully reminds the Examiner that there must have been a reasonable expectation of obtaining what is claimed, thus requiring that those in the art reasonably **expect** that identification of blood vessel related genes involved in blood vessel growth in zebrafish can be achieved, not just that such identification might be possible. It is hindsight to say that such an expectation would have been present based on the present record. Thus, Applicants believe that claims 13 and 14 are unobvious over the combination of Motoike et al. and Matz et al. and respectfully request withdrawal of this rejection.

Pursuant to the above amendments and remarks, consideration and allowance of the pending application is believed to be warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

A Credit Card Payment Form PTO-2038 authorizing payment in the amount of $510.00 representing the fee for small entity under 37 C.F.R. § 1.17(a)(3) and a Request for Extension of Time are enclosed. This amount is believed to be correct; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

NEEDLE & ROSENBERG, P.C.



Lizette M. Fernandez, Ph.D.
Registration No. 46,696

NEEDLE & ROSENBERG, P.C.
Customer Number 23859
(678) 420-9300
(678) 420-9301 (fax)

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Lizette M. Fernandez

8/13/07
Date